A Predictive Model for Massive Transfusion in Combat Casualty Patients

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Background: Massive transfusion (MT) is associated with increased morbidity and mortality in severely injured patients. Early and aggressive use of blood products in these patients may correct coagulopathy, control bleeding, and improve outcomes. However, rapid identification of patients at risk for MT has been difficult. We postulated that evaluation of clinical variables routinely assessed upon admission would allow identification of these patients for earlier, more effective intervention.

Methods: A retrospective cohort study was conducted at a single combat support hospital to identify risk factors for MT in patients with traumatic injuries. Demographic, diagnostic, and laboratory variables obtained upon admission were evaluated. Univariate and multivariate analyses were performed. An algorithm was formulated, validated with an independent dataset and a simple scoring system was devised.

Results: Three thousand four hundred forty-two patient records were reviewed. At least one unit of blood was transfused to 680 patients at the combat support hospital. Exclusion criteria included age less than 18 years, transfer from another medical facility, designation as a security internee, or incomplete data fields. The final number of patients was 302, of whom 26.5% (80 of 302) received a MT. Patients with MT had higher mortality (29 vs. 7% [*p* < 0.001]), and an increased Injury Severity Score (25 ± 11.1 vs. 18 ± 16.2 [*p* < 0.001]). Four independent risk factors for MT were identified: heart rate >105 bpm, systolic blood pressure <110 mm Hg, pH <7.25, and hematocrit <32.0%. An algorithm was created to analyze the risk of MT (area under the curve [AUC] = 0.839). In an independent data set of 396 patients the ability to accurately identify those requiring MT was 66% (AUC = 0.747).

Conclusions: Independent predictors for MT were identified in a cohort of severely injured patients requiring transfusions. Patients requiring a MT can be identified with variables commonly obtained upon hospital admission.

Key Word: Massive transfusion.

Trauma is the leading cause of death in persons under the age of 40 and severe hemorrhage is a major source of mortality in both civilian and military trauma.[1–4] Death from traumatic exsanguination usually occurs rapidly, typically in the first 6 hours to 12 hours.[5–7] Approximately 10% of all injured patients are transfused one or more units of blood and up to 30% of these require a massive transfusion (MT) defined as 10 or more units of blood in the first 24 hours of admission.[8,9] Although transfusion may be necessary to improved tissue oxygenation, multiple studies have shown blood transfusion to be associated with poor outcomes including increased rate of infection, acute lung injury and acute respiratory distress syndrome, multiple system organ failure, and death.[9–16]

In addition to acute hemorrhage, hypothermia, acidosis, and coagulopathy have been demonstrated to perpetuate the ongoing cycle of bleeding.[17] Recent studies have demonstrated that the acute coagulopathy of trauma is often present before any resuscitative efforts.[18,19] This has led to an ongoing reevaluation of traditional resuscitation practices for severely injured patients, focusing on limiting the amount of crystalloid and packed red blood cells (RBC) whereas increasing the ratio of transfused plasma and platelets.[20–23]

Early identification of the patients at risk for MT may be of use to direct rapid correction of coagulopathy, acidosis, and hypothermia and allow for early mobilization of blood bank resources and in military facilities, activation of whole blood donation.[24,25] Predictive models for MT have been developed in liver transplantation and cardiac surgery.[26,27] These models are primarily based upon preoperative laboratory values and patient demographics but also include such values as duration of cardiopulmonary bypass and cause of liver failure. These latter variables demonstrate a contrast between the controlled environment of planned surgery and the emergent interventions associated with trauma surgery. Recently, predictors for MT in both civilian and military trauma patients have been produced and other studies are currently ongoing.[28–30] We proposed that a model based upon physiologic and laboratory values available soon after arrival to the emergency department may identify those combat casualty patients at greatest risk for requiring a MT.

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METHODS

An Institutional Review Board-approved retrospective review of all patients treated at a single combat support hospital from September 2003 through December 2004 was performed. Data were obtained from the Joint Theater Trauma Registry (JTTR) maintained at the United States Army Institute of Surgical Research. The JTTR is a Department of Defense database established to prospectively collect data from multiple clinical and administrative systems. Demographic, laboratory and physiologic data, as well as transfusion requirements and outcomes were obtained. In the event of missing laboratory data the individual charts were reviewed by two authors (D.F.M. and S.E.M.) using the Patient Administration Systems and Biostatistics Activity database. Blood transfusions consisted of packed RBCs, fresh whole blood, or a combination of both. Transfusion requirements were obtained from the JTTR and MT and was defined as ≥10 units of blood in the initial 24 hours after admission. Patients were excluded from the study if they were not transfused at least one unit of blood in the initial 24 hours after presentation to the hospital. Additional exclusion criteria were treatment at another medical facility before transfer to the combat support hospital, age younger than 18 years, or designation as a security internee.

Variables submitted for univariate analysis were age, systolic blood pressure (SBP), diastolic blood pressure, heart rate (HR), temperature, Glasgow Coma Score, hematocrit (Hct), prothrombin time (PT), International Normalization Ratio (INR), pH, and base deficit (BD). Variables were assigned dichotomous status based on the difference between the mean value of the MT group and that of the nonmassively transfused group. The mean was determined for each variable for both the MT and non-MT groups. The median value between the means was used to predict likelihood of MT. Univariate analysis was performed with inclusion of all variables with p value ≤0.2. Colinearity was investigated and if present, the less strongly associated variable was eliminated. Multivariate stepwise logistic regression analysis was performed. The discriminant values were then modified to more clinically identifiable values and the multivariate analysis was again performed. A validation group of patients treated at the same combat support hospital from the period of December 2004 through October 2005 were subjected to the same predictive equation and the receiver operator curve (ROC) value was determined. A simple scoring system based on aggregate number of predictive variables present at the time of admission was created.

Continuous variables were compared with a Student's t test and categorical variables were described with χ^2 analysis. Microsoft Office Excel 2003 (Microsoft Corp, Redmond, WA) was used for database construction and comparison. Model construction was performed with SPSS 14.0 (Cary, NC). Variables are expressed as mean ± SD and statistical significance was set for a p value less than 0.05.

RESULTS

During the study period 3,442 patients were treated at the single combat support hospital. Of these, 680 (19.8%) received at least one unit of blood (either packed RBCs, fresh whole blood, or a combination of the two) in the first 24 hours of their admission. Patients were excluded for having received medical care at another medical treatment facility before transfer to the combat support hospital (n = 204), being under the age of 18 years (n = 29), being designated a security internee (n = 81), or having incomplete datasets (n = 44). The remaining 302 records were used for model development. Eighty of the 302 (26%) received a MT. The MT group had a higher Injury Severity Score (ISS) (25 ± 11.1 vs. 18 ± 16.2, $p < 0.001$) and in-hospital mortality (29 vs. 7%, $p < 0.001$) compared with the nonmassively transfused patients (Fig. 1). Figure 2 demonstrates the number of patients receiving each integer unit of blood. The most frequent numbers of units transfused were two units (n = 63) and four units (n = 61). Although comprising only 26% of the study population, the MT group received 63% of all transfusions (1,479 of 2,360 units) (Fig. 3).
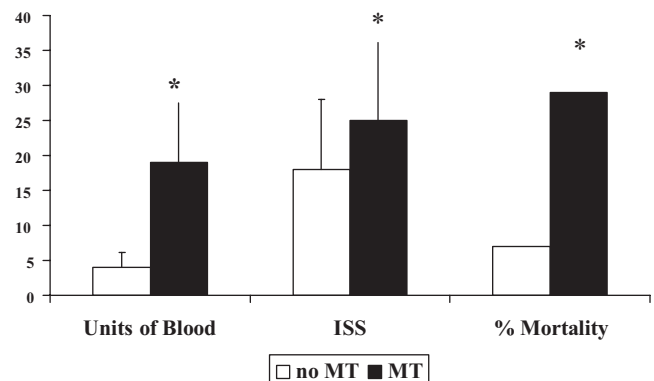
Fig. 1. *Comparison of massive transfusion (MT) patients to those that did not receive a massive transfusion (no MT). The massive transfusion patients had significantly higher transfusion requirement, Injury Severity Score and in-hospital mortality compared with those patients who were not massively transfused.* *p < 0.001.
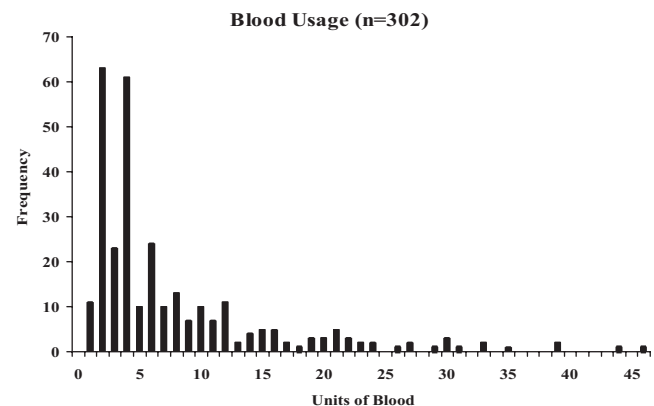
Fig. 2. *Histogram of the number of patients receiving each number of units of blood.*

% of Total Blood Usage
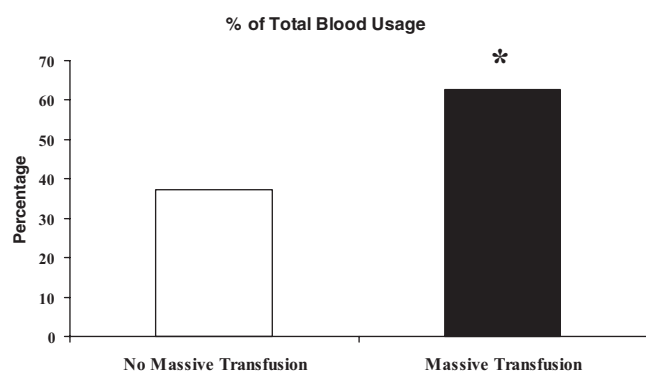
Fig. 3. *Percentage of total transfused blood. Patients receiving a massive transfusion account for 26% of the study population and consumed 63% of the total 2,360 units of blood transfused. *p < 0.001.*

Table 1 **Means for Variables Entered Into Multivariate Stepwise Logistic Regression**

	No MT	MT
Age (yr)	28 ± 10.4	28 ± 8.3
Glasgow Coma Score	12 ± 4.8	11 ± 5.0
HR (bpm)	95 ± 24.0	117 ± 26.5*
SBP (mm Hg)	120 ± 25.2	94 ± 28.2*
Diastolic blood pressure (mm Hg)	66 ± 17.7	52 ± 17.0*
Temp (°F)	96.9 ± 1.92	95.7 ± 2.50*
Hct (% volume)	34.6 ± 7.42	30.0 ± 8.50*
pH	7.30 ± 0.10	7.16 ± 0.18*
BD (mmol/L)	4 ± 4.4	10 ± 7.7*
PT (s)	16 ± 4.8	18 ± 8.9*
INR	1.5 ± 0.49	2.0 ± 1.29*

The difference between the mean of the massive transfusion group and that of the mean of the nonmassively transfused group was used to assign the classed variables for model development.

*$p < 0.05$.

Univariate analysis was performed for the following variables: age, SBP, diastolic blood pressure, HR, temperature, Glasgow Coma Scale, Hct, PT, INR, pH, and BD (Table 1). All variables with the exception of age and Glasgow Coma Scale were independently associated with MT and entered into the multivariate analysis. Multivariate stepwise logistic regression analysis was performed yielding the variables of HR ≥107 beats per minute, SBP ≤108 mm Hg, pH ≤7.23, and Hct ≤32.4% with a ROC value of 0.843 (95% confidence interval: 0.792–0.895). The values of the variables were then reassigned to facilitate ease in application and the predictive model was recalculated (Table 2). The final values of HR >105 beats per minute, SBP <110 mm Hg, pH <7.25, and Hct <32.0% yielded a ROC value of 0.839 (95% confidence interval: 0.787–0.891). The Wald values (Table 3) demonstrate the relative weighted influence of each variable. The final predictive equation was log $(p/[1 - p]) = 1.576 + (0.825 \times SBP) + (0.826 \times HR) + (1.044 \times Hct) + (0.462 \times pH)$, where variables have the value of either 0 or

Table 2 **Clinically Based Classed Variables**

	Average of Means	Clinical Discriminant	No MT	MT
HR (bpm)	107	105	>105	<106
SBP (mm Hg)	108	110	<110	>109
Hct (% volume)	32.4	32.0	<32.0	>31.9
pH	7.23	7.25	<7.25	>7.24

The variables were reassigned clinical endpoints of more simplicity and the model was tested against the new variables.

Table 3 **Results of Multivariate Logistic Regression Analysis**

	Wald Value	Coefficient	Standard Error	Odds Ratio
HR > 105 bpm	23.77	1.58	0.32	4.8
SBP < 110 mm Hg	14.96	1.26	0.33	3.5
pH < 7.25	14.09	1.23	0.33	3.4
Hct < 32%	2.33	0.49	0.32	1.6

1 based on whether or not the value is classed as predictive. The positive and negative predictive values are 66% and 72%, respectively, (Table 4).

The model was validated against a population of patients treated at the same combat support hospital from December 2004 through October 2005 using the same inclusion and exclusion criteria yielding an area under the ROC of 0.747. The basic characteristics of the model development set and the validation set are shown in Table 5.

In an unweighted analysis of the four predictive variables, incidence of MT increased from 20% if the patient had one of the values present of arrival to 80% if all four values

**Table 4** **Statistical Outcomes of Predictive Model on Validation Set**

Test	Value (%)
Sensitivity	59.4
Specificity	77.4
PPV	66.4
NPV	71.7

PPV indicates positive predictive value; NPV, negative predictive value.

Table 5 **Basic Characteristics of the Model Development Data Set and the Validation Data Set**

	Development Set	Validation Set	p
Number	302	396	NS
Age (yr)	28 ± 9.8	29 ± 9.6	NS
Male	285 (94%)	383 (97%)	NS
ISS	20 ± 10.7	25 ± 22.1	<0.001
Units of blood	8 ± 8.0	12 ± 13.9	<0.001
Massive transfusion (n, %)	80 (26)	170 (43)	<0.001

ISS indicates Injury Severity Score; NS, not significant.
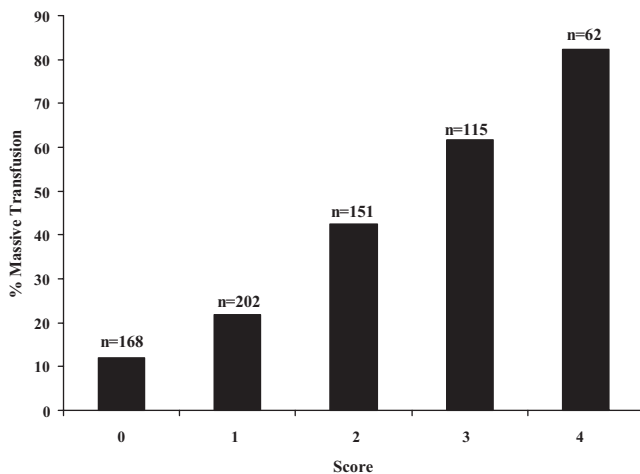
Fig. 4. *Observed percentage of massive transfusion for each number of variables with values associated with massive transfusion.*

were present (Fig. 4). However, patients who had none of the four values upon admission still had an 11% incidence of MT.

DISCUSSION

Hemorrhage is a major cause of mortality in the injured patient, and exsanguination has been shown to be the leading cause of death in the first hour after injury.[5] Recently a study investigating deaths in this initial hour found that up to 38% were potentially survivable as defined as an injury to a single organ or vessel.[6] These findings demonstrate the necessity of prompt control of hemorrhage. Currently, resuscitation strategies in severely injured patients are being reexamined. By addressing the early coagulopathy of trauma and acidosis promptly by limiting crystalloid infusion and augmenting the traditional resuscitation practice of packed RBC transfusion with early and increased use plasma and platelets, the focus is as much on providing a suitable intravascular milieu as it is on prompt surgical intervention.[20,21] This approach has been called damage control resuscitation.

Allogeneic RBC transfusion has long been known to have detrimental consequences. Before the advent of medical immunosuppression, intentional immunosuppression before organ transplantation was accomplished with scheduled RBC transfusions.[31] Research has since demonstrated that transfusion primes the immune system to excessively activate nonspecific proinflammatory cascades while decreasing the overall ability to mount an organized, effective defense to infection.[32–36] Transfusion has also been shown to increase rates of nosocomial infections, multiple system organ failure, acute lung injury and acute respiratory distress syndrome, and mortality.[9–16,37] Consequently, transfusion of RBCs is now limited to those patients with a demonstrated need for increased oxygen carrying capacity.

In accordance with previous studies, we found that the bulk of the blood transfused was used by the minority of the patients and conversely, many patients received a small

amount of blood.[8] In our study, massively transfused patients comprised 26% of the population and consumed 63% of all the blood whereas more than half of the patients (52%) received four or fewer units. The majority of patients receive a small amount of blood that likely does little to improve oxygen delivery, but exposes them to the detrimental effects of an allogeneic transfusion. Do all of these patients need blood or are they perhaps unnecessarily being exposed to potential harm? An accurate model predicting which patients are at the highest risk for MT may benefit both populations. In addition to identifying the patients at greatest need for MT a useful algorithm may also identify those patients who do not require a substantial amount of blood. This may lead to foregoing transfusion in these patients thus reducing the number of patients receiving the commonly transfused two or four units of blood.

Ongoing efforts to identify those casualties at greatest risk for MT may be helpful in early mobilization of the resources required to deliver the currently recommended components of an optimal MT guideline, 1 unit of RBCs: 1 unit of plasma: 1 unit of platelets.[38] Based upon the likelihood of MT the liberal use of plasma and platelets as well as possible adjuncts such as factor VII may be warranted.[39] Activation of the blood banking resources including warming of blood products, cross matching, and physically delivering the products to the Emergency Department or operating room may be initiated soon after the patient arrives. Earlier initiation of this MT guideline may prevent or correct the coagulopathy of trauma, leading to more effective surgical intervention and decreased mortality.

Previous studies in liver transplantation and cardiac surgery identified predictors of MT specific to these fields such as cause of liver failure and presence or absence of previous sternotomy.[26,27] These studies are primarily based on information attainable before the intervention thus allowing for proper planning. The major difference in these elective surgery models is that they pertain to circumstances in which the source of hemorrhage is known, as opposed to trauma, where the surgeon is frequently presented with a hypothermic, coagulopathic patient in shock, suffering from multiple injuries. A useful model for MT in trauma must be based on information that is rapidly available, concrete, and simply applicable. In the current study several physiologic and laboratory variables that are readily available were evaluated. Admission vital signs are available within seconds of arrival to the Emergency Department and are often reported from the field before arrival. The laboratory tests analyzed in this study are also promptly available. Hct, hemoglobin, pH, and BD are all available on a single i-STAT cartridge (Abbott Laboratories, Abbott Park, IL) whereas coagulation data such as INR may be obtained simultaneously on a second cartridge and these values are available in 2 minutes.

A measure of acidosis remains in the final model whereas indicators of the other aspects of the "lethal triad", hypothermia, and coagulopathy, did not. This is true for the

Table 6 **Variables for Predictive Models of Massive Transfusion**

Study	Physiology/Laboratory	Anatomic	ROC Value
McLaughlin et al.	HR, SBP, pH, Hct	—	0.839
Yücel et al.	HR, SBP, BD, Hgb	Male, +FAST, long bone/pelvic fracture	0.892
Schreiber et al.	Hgb, INR	Penetrating mechanism	0.804

Hgb indicates hemoglobin concentration; BD, base deficit; FAST, Focused Assessment Sonography in Trauma; INR, International Normalization Ratio.

recent civilian study as well; however the Yücel group did not include a measure of coagulation or temperature in their initial variable set (Table 5).[28] A recent study based upon military casualties identified coagulopathy (INR) as a contributing factor to the need for MT.[29] Because of standardization in prehospital care it may be that the difference in mean temperature between the MT group and non-MT group upon arrival was similar enough that a significant difference between the two groups could not be analyzed. Also the INR value was the most commonly absent variable in the initial assessment of parameters, thus introducing possible bias. That hypothermia and coagulopathy are not present in the predictive model based on parameters present at the time of admission does not necessarily mean that temperature and coagulopathy do not play an important role in hemostasis and transfusion requirements. These values may be affected throughout the resuscitation and are frequently altered intraoperatively.

Identifying the midpoint between the means for the MT group and the no MT group allowed for setting a value to assign the likelihood of receiving an MT. The values used to generate the model were then rounded to the nearest clinically useable value. SBP less than 110 mm Hg was predictive of MT, as were HR above 105 bpm, pH below 7.25, and Hct below 32.0%. These values are more practical for immediate recall and application than SBP less than 108 mm Hg, HR above 107 bpm, pH less than 7.23, and Hct less than 32.4%. In rounding to a more memorable value a small loss in predictive power was encountered (0.843–0.839). We think that this is acceptable as it facilitates usage.

Of the values for the four indicators described in this article not all appear particularly ominous. A SBP of 109 mm Hg may not elicit the same level of concern as a pH of 7.24 however they are virtually identical in their predictive capacity. Recently, in a study reviewing the National Trauma Data Bank, Eastridge et al. identified the blood pressure at admission associated with increased mortality to be approximately 110 mm Hg, far above the standard reference for shock of 90 mm Hg.[40] Studies such as the Eastridge study, the Yücel study (which assigns significant point values for SBP below 120 mm Hg and greater still for SBP less than 100 mm Hg) and our study continue to demonstrate increased morbidity and mortality at SBPs much higher than previously considered indicative of "hypotension" or shock.

Though based on combat casualties our model corresponds with previous findings in civilian populations (Table 5). However, one advantage of the current study is that it does not rely on interpretation or provider expertise. The Yücel model includes intraabdominal free fluid by Focused Assessment Sonography in Trauma (FAST) examination (Table 6). In many studies FAST has been shown to be extremely sensitive for hemoperitoneum but it is nonetheless operator dependent and has been shown to be very unreliable in other studies. Friese et al. performed a review of the ability of FAST to diagnose hemperitoneum in patients with pelvic fractures and found a sensitivity of only 26% and a specificity of 96%.[41] Blackbourne et al. found a sensitivity of 31% on initial FAST examination for identifying intraabdominal injury, though the sensitivity improved to 71% on secondary examination.[42] Although the accuracy of FAST can be argued, it is a subjective, learned skill with potential for error. The current study simply evaluates four objective parameters easily assessed within minutes of admission with no need for technical training.

In contrast to the Yücel study population in which 95% of the patients were injured by blunt mechanisms and approximately one fourth of the patients were women the patients in this study were nearly exclusively men and injured with penetrating mechanisms. The mean ISS was relatively similar with the Yücel group's development data set having a mean ISS of 25 and the current study with a mean ISS of 20. Our study however had approximately twice the rate of MT (26% vs. 14%). Also, the military trauma system is different from civilian systems in that the combat support hospitals are limited in the total amount of stored blood products and frequently initiate whole blood donations.[24,25] In the austere environments of military conflicts the ability to identify these patients early and mobilize resources or relocate the patient to a facility with these resources available is of significant utility.

This study is limited by the constraints inherent to all retrospective studies. Mortality data are only that for in-hospital mortality and did not include long-term data for Iraqi national patients or deaths after evacuation. For these reasons mortality was not a main outcome. Completeness and fidelity of data collected is always of concern. The JTTR is regularly reviewed but many fields were not collected or documented. Potential provider bias is introduced in the decision of which tests ordered. Some patients with minimal transfusion requirements (<4 units) did not have pH, BD, PT, or INR documented on arrival. This may reflect that the provider did not view the patient as being in extremis and did not order the tests. However, some of the more seriously injured and more

highly transfused patients did not have preoperative labs drawn either as they progressed directly to the operating room. Another concern is that the model development group and the validation group are significantly different in many key areas including ISS, total transfusion, and percent requiring MT. As the current military conflict has progressed the average ISS has increased making the validation group a more severely injured and higher transfused group. These differences in populations may have contributed to a decreased sensitivity and positive predictive value. Prospective studies with this model and other variants to establish the efficacy, sensitivity, and specificity are warranted. Although a 66% positive predictive value does not appear clinically useful, in light of the fact that half of all packed red blood cells transfused are administered to patients that may not need them any improvement in defining patients requiring MT is of benefit.

In this study we have demonstrated that MT is associated with high injury severity and poor clinical outcomes and that patients requiring MTs consume substantial blood banking resources. We conclude that a predictive model for the need of MT in trauma patients can be formulated from simple variables that are quickly attained upon arrival potentially allowing for earlier, more effective intervention with optimal MT guidelines.

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DISCUSSION

Dr. Steven E. Wolf (University of Texas Health Science Center, San Antonio, TX): This is an excellent study providing us with information on who is likely to require massive transfusion in combat-related injuries. The authors point out that with information gathered routinely at admission, they can predict somewhere between 66% and 83% of who will require massive transfusion. This is very important information that potentially gives freedom for providers to deviate from established resuscitation algorithms toward aggressive early use of blood products with the assumption that early product use improves outcomes. One envisions the scenario that someone who arrives in shock by vital signs and is acidotic and anemic should immediately receive blood rather than poisonous crystalloid or colloid. My first question is this, when did these men and women first receive blood products? How much did they receive in the resuscitation bay? Did this correlate with outcomes? This should address the assumption above. Second, to turn the data on its head, some patients receiving massive transfusion did not meet these criteria. Was their injury pattern different from your predicted population? For instance, did they have more head injuries? Lastly, in your scoring system, there appears to be a linear increase in the rate of massive transfusion with the addition of sentinel variables. Almost universally, biologic systems in responses such as these follow a sigmoid or logarithmic curve with additional indicators of injury indicating a cut point if you will for a robust physiologic response. Why don't we see that here? Thank you again for an excellent study, which I believe should alter practice for many of us.

Dr. Daniel F. McLaughlin (US Army Institute of Surgical Research, Fort Sam Houston, TX): Thank you, Dr. Wolf, for the insightful comments and questions. In regards to your inquiry as to when and where the transfusions occurred and if this influenced outcome, our database does not include the timing or setting of transfusion but rather only the total 24 hour transfusion requirement in all settings, including the emergency department, operating room and intensive care unit. With this current dataset we are unable to ascertain whether early transfusion improved survival but additional datasets are becoming available that are more detailed in respect to the timing of transfusions. This is an interesting point to consider and warrants investigation.

The second question pertaining to the injury pattern of those patients who received a massive transfusion but had none of the predictive parameters at admission to the ED is also quite interesting. The patients with one or more of the predictive values present at admission had significantly higher thoracic and abdominal injuries compared with those with none of the predictive values present but still received massive transfusion. There was no difference in severity of injury to the head or brain.

Lastly, the point of a linear increase rather than a sigmoidal or logarithmic curve in our observed incidence of massive transfusion per total number of aggregate variables present is explained by the relatively small number of points observed. In the Yücel article the variables were weighted and assigned appropriate value. A total of 0 to 28 was devised. The observed and predicted incidence of MT followed a sigmoid distribution. We think the same would be true if a weighted, rather than unweighted system were to be used with our data. The strength of heart rate is approximately 10 times that of hematocrit. (Table 3) If a weighted system were to be produced with heart rate greater than 105 bpm contributing 10 points and hematocrit less than 32 contributing 1 point (and likewise 7 points each for systolic blood pressure and pH) a total score could range from 0 to 25. In our study we report the observed rate of MT by total parameter present; total scores ranging from 0 to 4. We knowingly sacrificed precision for simplicity and have created a set of variables that may be used to rapidly assess the likelihood of requiring a massive transfusion.